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(54) Title: NOVEL CRYSTALLINE FORM

(57) Abstract: The present invention relates to a novel crystalline form of the *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid. Further, the present invention also relates to processes for preparing it.

NOVEL CRYSTALLINE FORM

Field of the invention

The present invention relates to a novel crystalline form of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid. Further, the present invention also relates to processes for preparation thereof, pharmaceutical formulations comprising it and its use as active ingredient in the manufacture of a medicament for use in treatment of clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance or with other manifestations of the metabolic syndrome and to methods for their therapeutic use.

Background of the invention and prior art

In the formulation of drug compositions, it is important for the drug substance to be in a form in which it can be conveniently handled and processed. This is of importance, not only from the point of view of obtaining a commercially viable manufacturing process, but also from the point of view of subsequent manufacture of pharmaceutical formulations comprising the active compound.

Further, in the manufacture of oral drug compositions, it is important that a reliable, reproducible and constant plasma concentration profile of drug is provided following administration to a patient.

Chemical stability, solid state stability, dissolution rate poperties and "shelf life" of the active ingredients are also very important factors. The drug substance, and compositions containing it, should be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the physico-chemical characteristics of the active component, e.g. its chemical composition, density, hygroscopicity and solubility.

Amorphous materials may present problems in this regard. For example, such materials are typically more difficult to handle and to formulate, provide for unreliable solubility, and are often found to be more unstable.

Thus, in the manufacture of commercially viable and pharmaceutically acceptable drug compositions, it is important, wherever possible, to provide the drug in a substantially crystalline and stable form.

Previously, certain (2*S*)-3-(4-{2-[amino]-2-oxoethoxy}phenyl)-2-ethoxypropanoic acid derivatives were disclosed in WO 03/051821 A1.

Salts of the (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid were disclosed in WO 2004/110984 A1. In that application a crystalline polymorf with the XRPD pattern given in Ex. 6, Figure C (on p. 35), was disclosed; a polymorph hereinafter referred to as "Form I".

Brief description of the drawings

Figure 1 is an X-ray powder diffractogram of the *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid, Form III.

Figure 2 is an X-ray powder diffractogram of the *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid, Form I.

Figure 3 is an X-ray powder diffractogram of the *tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid, Form II.

Description of the invention

It has now surprisingly been found that the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid exists in further crystal forms.

One such form is a substantially X-ray amorphous form, referred to as "Form II", having the XRPD pattern as dislosed in Figure 3.

Another such crystal form can be obtained when preparing this t-butylamine salt at higher temperatures than previously. This crystal form is hereinafter also referred to as "Form III", which forms part of this invention, is having the XRPD pattern as dislosed in Figure 1.

The notation "Form III" relates to the order in time in which the forms were created, not to their relative thermodynamic stability.

It is thus an object of the present invention to provide a crystalline form of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid with advantageous properties.
This crystalline form can be crystallized at elevated temperatures, specifically at or above 35° C, even up to around 75° C.

The compound of the invention has the advantage that it is believed to be the presently known most termodynamically stable form. Thus giving improved chemical and solid state stability with the effect that the compound may be stable when stored over prolonged periods.

The *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid Form III is a crystalline form also exhibiting advantageous properties, such as convenient handling.

Form III further has the advantage of being manufacturable at elevated temperatures, thus giving process advantages like higher yields and avoiding thick slurries obtained at lower

temperatures and less consumption of solvents due to increased solubility with higher temperature of solvents, ease of achieving supersaturation by temperature decrease, etc. Crystallization of the compound of the present invention from an appropriate solvent system, containing at least one solvent, may be achieved by attaining supersaturation in a solvent system by solvent evaporation, by temperature decrease, and/or via the addition of anti-solvent (i.e. a solvent in which the compounds of the invention are poorly soluble).

The solvent system utilized in the crystallisation process may be one single solvent or a mixture of solvents. However, it is preferred that the crystallization is made from a mixed solvent system.

The *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid Form III is obtained upon crystallization from isopropyl acetate at tempertures at or above 35°C, e.g. 45°C or 72°C.

The Form I disclosed in WO 2004/110984 A1 is obtained upon crystallization at room temperature from acetone and isooctane.

The compound/polymorf of the invention can be incorporated into pharmaceutical formulations for later administration to patients in need thereof.

Detailed description of the invention

The *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid Form III, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 1, exhibiting substantially the following d-values and intensities;

d-value (Å)	Relative intensity	Comment

19.0	**vs**	
11.6	m	
8.2	**s**	
6.0	**s**	
5.7	m	
5.6	**m**	
5.4	m	
5.3	m	
5.3	m	
5.00	w	
4.77	**m**	
4.57	m	
4.48	m	
4.44	m	
4.34	m	
4.26	m	Broad
4.08	m	
3.81	m	
3.75	m	Very broad
3.30	w	
3.05	w	

Definitions used:

% Relative intensity*	Definition
70-100	vs (very strong)
32-70	s (strong)
14-32	m (medium)

5-14	w (weak)
<5	vw (very weak)

*The relative intensities are derived from diffractograms measured with variable slits.

The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the diffractogram of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid Form III.

The Form III of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid, is characterized in providing an X-ray powder diffraction pattern exhibiting peaks at substantially the following d-values: 4.77, 5.6, 6.0, 8.2 and 19.0 Å.

More preferably, the Form III of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid, is characterized in providing an X-ray powder diffraction pattern exhibiting peaks at substantially the following d-values: 3.81, 4.48, 4.57, 4.77, 5.3, 5.4, 5.6, 5.7, 6.0, 8.2, 11.6 and 19.0 Å.

Most preferably, the Form III of the tert-butylamine salt of (2S)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid, is characterized in providing an X-ray powder diffraction pattern exhibiting peaks at substantially the following d-values: 3.05, 3.30, 3.75, 3.81, 4.08, 4.26, 4.34, 4.44, 4.48, 4.57, 4.77, 5.00, 5.3, 5.4, 5.6, 5.7, 6.0, 8.2, 11.6 and 19.0 Å.

NMR data from the polymorf of the invention, the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid Form III;

^{1}H-NMR (500 MHz, $CDCl_3$):
7.4-7.1 (7H, m), 6.9 (1H, d), 6.7 (1H, d), 4.7 (1H, s), 4.4 (1H, s), 3.8 (1H, m), 3.7 (1H, m), 3.6 (2H, m), 3.4 (1H, t), 3.2 (2H, m), 3.0 (1H, m), 2.9 (3H, m), 1.6 (2H, br m), 1.4 (9H, br s), 1.3 (6H, br m), 1.1 (3H, t), 0.9 (3H, m)

The Form III has been shown to be an ansolvate (/anhydrate) with TGA and GC methodology.

Solvent systems

Crystallization of the compound of the present invention from an appropriate solvent system, containing at least one solvent, may be achieved by attaining supersaturation in a solvent system by solvent evaporation, by temperature decrease, and/or via the addition of anti-solvent (i.e. a solvent in which the compounds of the invention are poorly soluble).

As solvent are suitably used liquid aliphatic ketones or liquid aliphatic esters, preferably at room temperature liquid aliphatic ketones or at room temperature liquid aliphatic esters, more preferably at room temperature liquid aliphatic ketones or at room temperature liquid aliphatic esters, most preferably at room temperature aliphatic liquid ketones or esters selected from the group consisting of isopropylacetate or methyl-isobutyl-ketone.

It is also contemplated that ketones or esters that are solid at room temperature but liquid at higher temperatures, i.e. those having a melting point below the lowest process temperature, can be utilized in the processes of the invention, either alone or mixed with solvents liquid at room temperature.

As anti-solvents are suitably used a low-polar or non-polar solvents, preferably aliphatic alkanes or aliphatic ethers, more preferably at room temperature liquid aliphatic alkanes or at room temperature liquid aliphatic ethers, and most preferably at room temperature liquid aliphatic alkanes or at room temperature liquid aliphatic ethers selected from the group consisting of isooctane (2,2,4 –trimethylpentan), n-hexan, petroleum ether and t-butyl-methyl-ether.

Crystallization of the compound of the present invention can be achieved starting from pure *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid of any polymorphic form, or mixtures of any forms thereof.

Whether ansolvate or solvate crystallizes is related to the kinetics and equilibrium conditions of the respective forms at the specific conditions. Thus, as may be appreciated by the skilled person, the crystalline form that is obtained depends upon both the kinetics and the thermodynamics of the crystallization process. Under certain thermodynamic conditions (solvent system, temperature, pressure and concentration of compound of the invention), one crystalline form may be more stable than another (or indeed any other). However, crystalline forms that have a relatively low thermodynamic stability may be kinetically favored. Thus, in addition, kinetic factors, such as time, impurity profile, agitation, the presence or absence of seeds, etc. may also influence which form that crystallizes.

Process

The *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid Form III is obtained upon crystallization from isopropyl acetate at tempertures at or above 35°C, e.g. 45°C or 72°C.

The Form I disclosed in WO 2004/110984 A1 is obtained upon crystallization at room temperature from acetone and isooctane.

In order to ensure that a particular crystalline form is substantially free from other crystal and non-crystal forms of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid it is prepared in the substantial absence of other crystalline forms, such that crystallization is preferably carried out by seeding with seed crystals of the desired crystalline form.

The tert-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid Form III, obtained according to the present invention is substantially free from other crystal and non-crystal forms of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid.

The term "substantially free from other crystal and non-crystal forms of the tert-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid" shall be understood to mean that the desired crystal form of this t-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid. contains less than 40%, preferably less than 20%, more preferably less than 10% of the sum of any other crystal or non-crystal forms of the tert-butyl-amine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid.

One object of the present invention is to provide processes for the preparation of Form III of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid.

In one aspect of the processes of the invention, crystallization is initiated and/or effected without seeding with crystals.

In another aspect of the processes of the invention, crystallization is initiated and/or effected with seeding with crystals of the appropriate crystalline form, i.e. Form III, of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid.

The process is characterized by comprising the following steps;
I) having the (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid dissolved in a suitable solvent or solvent mixture and adding tert-butylamine
II) optionallly adding an anti-solvent or anti-solvent mixture
III) adjusting the temperature to a temperature at or above 35°C
IV) stirring for at least 15-25 hours or more
V) separating off the product
VI) optionally washing with a suitable solvent
VII) drying the product

Or

I) having the (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid dissolved in a suitable solvent or solvent mixture and adding tert-butylamine

II) optionallly adding an anti-solvent or anti-solvent mixture

III) adjusting the temperature to a temperature at or above 35°C

IV) seeding with Form III at any stage after step I)

V) cooling the mixture slowly at a temperature decreasing rate not higher than 15°C/hour

VI) separating off the product

VII) optionally washing with a suitable solvent

VIII) drying the product

Or

I) having the (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid dissolved in a suitable solvent or solvent mixture and adding tert-butylamine

II) optionallly adding an anti-solvent or anti-solvent mixture

III) adjusting the temperature to a temperature at or above 35°C

IV) cooling the mixture slowly at a temperature decreasing rate not higher than 15°C/hour

V) separating off the product

VI) optionally washing with a suitable solvent

VII) drying the product

Or

I) having the (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid dissolved in a suitable solvent or solvent mixture and adding tert-butylamine

II) optionallly adding an anti-solvent or anti-solvent mixture

III) adjusting the temperature to a temperature at or above 35°C

IV) stirring for at least 15-25 hours or more

V) cooling the mixture slowly at a temperature decreasing rate not higher than 15°C/hour

VI) separating off the product

VII) optionally washing with a suitable solvent

VIII) drying the product

Or

I) having the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid or any polymorpic form thereof dissolved in a suitable solvent or solvent mixture

II) adjusting the temperature to a temperature at or above 35°C

III) optionallly adding an anti-solvent or anti-solvent mixture

IV) cooling the mixture slowly at a temperature decreasing rate not higher than 15°C/hour

V) optionally washing with a suitable solvent

VI) drying the product

The process is further characterized by that the ratio of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid to tert-butylamine is from 0.8:1 to 1.2:1 on equivalents basis or more preferably from 0.9:1 to 1.1:1 on equivalents basis or most preferred from 0.95:1 to 1.05:1 on equivalents basis.

Pharmaceutical formulations

The compound of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of a pharmaceutically acceptable dosage form, i.e. a pharmaceutical formulation. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compound of the invention in therapeutical treatment of humans are about 0.0001-100 mg/kg body weight, preferably 0.001-10 mg/kg body weight.

Oral formulations are preferred, particularly tablets or capsules which may be formulated by methods known to those skilled in the art, to provide doses of the active compound in

the range of 0.5mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25mg, 50mg, 100mg and 250mg.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including the compound of the invention in admixture with at least one pharmaceutically acceptable excipient, such as e.g., diluents and/or carriers.

Pharmacological properties

The compound of the invention is useful for the prophylaxis and/or treatment of clinical conditions associated with inherent or induced reduced sensitivity to insulin (insulin resistance) and associated metabolic disorders (also known as metabolic syndrome). These clinical conditions will include, but will not be limited to, general obesity, abdominal obesity, arterial hypertension, hyperinsulinaemia, hyperglycaemia, type 2 diabetes and the dyslipidaemia characteristically appearing with insulin resistance. This dyslipidaemia, also known as the atherogenic lipoprotein profile, is characterised by moderately elevated non-esterified fatty acids, elevated very low density lipoprotein (VLDL) triglyceride rich particles, high Apo B levels, low high density lipoprotein (HDL) levels associated with low apoAI particle levels and high Apo B levels in the presence of small, dense, low density lipoproteins (LDL) particles, phenotype B.

The compound of the present invention is expected to be useful in treating patients with combined or mixed hyperlipidemias or various degrees of hypertriglyceridemias and postprandial dyslipidemia with or without other manifestations of the metabolic syndrome. Treatment with the present compounds is expected to lower the cardiovascular morbidity and mortality associated with atherosclerosis due to their antidyslipidaemic as well as antiinflammatory properties. The cardiovascular disease conditions include macro-angiopathies of various internal organs causing myocardial infarction, congestive heart failure, cerebrovascular disease and peripheral arterial insufficiency of the lower extremities. Because of its insulin sensitizing effect the compound is also expected to prevent or delay the development of type 2 diabetes from the metabolic syndrome and diabetes of pregnancy. Therefore the development of long-term complications associated

with chronic hyperglycaemia in diabetes mellitus such as the micro-angiopathies causing renal disease, retinal damage and peripheral vascular disease of the lower limbs are expected to be delayed. Furthermore the compound may be useful in treatment of various conditions outside the cardiovascular system whether or not associated with insulin resistance, like polycystic ovarian syndrome, obesity, cancer and states of inflammatory disease including neurodegenerative disorders such as mild cognitive impairment, Alzheimer's disease, Parkinson's disease and multiple sclerosis.

The compound of the present invention is expected to be useful in controlling glucose levels in patients suffering from type 2 diabetes.

The present invention provides a method of treating or preventing dyslipidemias, the insulin resistance syndrome and/or metabolic disorders (as defined above) comprising the administration of the compound of the present invention to a mammal (particularly a human) in need thereof.

The present invention provides a method of treating or preventing type 2 diabetes comprising the administration of an effective amount of the compound of the present invention to a mammal (particularly a human) in need thereof.

In a further aspect the present invention provides the use of the compound of the present invention as a medicament.

In a further aspect the present invention provides the use of the compound of the present invention in the manufacture of a medicament for the treatment of insulin resistance and/or metabolic disorders.

Combination Therapy

The compound of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and

obesity. The compound of the invention may be combined with another therapeutic agent that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels of LDL-cholesterol. In patients with diabetes mellitus the compound of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

A compound of the invention may be used alongside other therapies for the treatment of metabolic syndrome or type 2 diabetes and its associated complications, these include biguanide drugs, for example metformin, phenformin and buformin, insulin (synthetic insulin analogues, amylin) and oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors). An example of an alpha-glucosidase inhibitor is acarbose or voglibose or miglitol. An example of a prandial glucose regulator is repaglinide or nateglinide.

In another aspect of the invention, the compound of the invention, may be administered in association with a PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma and/or delta agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art. These include the compounds described in WO 01/12187, WO 01/12612, WO 99/62870, WO 99/62872, WO 99/62871, WO 98/57941, WO 01/40170, WO 04/000790, WO 04/000295, WO 04/000294, WO 03/051822, WO 03/051821, WO 02/096863, WO 03/051826, WO 02/085844, WO 01/040172, J Med Chem, 1996, 39, 665, Expert Opinion on Therapeutic Patents, 10 (5), 623-634 (in particular the compounds described in the patent applications listed on page 634) and J Med Chem, 2000, 43, 527 which are all incorporated herein by reference. Particularly a PPAR alpha and/or gamma and/or delta agonist refers to muraglitazar (BMS 298585), rivoglitazone (CS-011), netoglitazone (MCC-555), balaglitazone (DRF-2593, NN-2344), clofibrate, fenofibrate, bezafibrate, gemfibrozil , ciprofibrate, pioglitazone, rosiglitazone, AVE-0847, AVE-8134, CLX-0921, DRF-10945, DRF-4832, LY-518674, LY-818, LY-929, 641597, GW-590735, GW-677954, GW-501516, MBX-102, ONO-5129, KRP-101, R-483 (BM131258), TAK-559 or TAK-654. Particularly a PPAR alpha

and/or gamma and/or delta agonist refers to tesaglitazar ((S)-2-ethoxy-3-[4-(2-{4-methanesulphonyl-oxyphenyl}ethoxy)phenyl]propanoic acid) and pharmaceutically acceptable salts thereof.

In addition the compound of the invention may be used in conjunction with a sulfonylurea for example: glimepiride, glibenclamide (glyburide), gliclazide, glipizide, gliquidone, chloropropamide, tolbutamide, acetohexamide, glycopyramide, carbutamide, glibonuride, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, tolcylamide and tolazamide. Preferably the sulfonylurea is glimepiride or glibenclamide (glyburide). More preferably the sulfonylurea is glimepiride. The present invention includes administration of a compound of the present invention in conjunction with one, two or more existing therapies described in this combination section. The doses of the other existing therapies for the treatment of type 2 diabetes and its associated complications will be those known in the art and approved for use by regulatory bodies for example the FDA and may be found in the Orange Book published by the FDA. Alternatively smaller doses may be used as a result of the benefits derived from the combination. The present invention also includes the compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to inhibitors of HMG-CoA reductase (3-hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin selected from the group consisting of atorvastatin, bervastatin, cerivastatin, dalvastatin, fluvastatin, itavastatin, lovastatin, mevastatin, nicostatin, nivastatin, pravastatin and simvastatin, or a pharmaceutically acceptable salt, especially sodium or calcium, or a solvate thereof, or a solvate of such a salt. A particular statin is atorvastatin, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof. A more particular statin is atorvastatin calcium salt. A particularly preferred statin is, however, a compound with the chemical name (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)-amino]-pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, [also known as (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[*N*-methyl-*N*-(methylsulfonyl)-amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] or a pharmaceutically acceptable salt or solvate thereof, or a solvate of such a salt. The compound (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl-(methylsulfonyl)-amino]-

pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid, and its calcium and sodium salts are disclosed in European Patent Application, Publication No. EP-A-0521471, and in Bioorganic and Medicinal Chemistry, (1997), 5(2), 437-444. This latter statin is now known under its generic name rosuvastatin.

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and metabolites, whether active or inactive.

The present invention also includes the compound of the present invention in combination with a bile acid sequestering agent, for example colestipol or cholestyramine or cholestagel.

The present invention also includes the compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor).

Suitable compounds possessing IBAT inhibitory activity have been described, see for instance the compounds described in WO 93/16055, WO 94/18183, WO 94/18184, WO 96/05188, WO 96/08484, WO 96/16051, WO 97/33882, WO 98/07449, WO 98/03818, WO 98/38182, WO 99/32478, WO 99/35135, WO 98/40375, WO 99/35153, WO 99/64409, WO 99/64410, WO 00/01687, WO 00/47568, WO 00/61568, WO 00/62810, WO 01/68906, DE 19825804, WO 00/38725, WO 00/38726, WO 00/38727, WO 00/38728, WO 00/38729, WO 01/68906, WO 01/66533, WO 02/32428, WO 02/50051, EP 864 582, EP489423, EP549967, EP573848, EP624593, EP624594, EP624595 and EP624596 and the contents of these patent applications are incorporated herein by reference. Further suitable compunds possessing IBAT inhibitory activity have been described in WO 94/24087, WO 98/56757, WO 00/20392, WO 00/20393, WO 00/20410, WO 00/20437, WO 01/34570, WO 00/35889, WO 01/68637, WO 02/08211, WO 03/020710, WO 03/022825, WO 03/022830, WO 03/022286, WO 03/091232, WO 03/106482, JP 10072371, US 5070103, EP 251 315, EP 417 725, EP 869 121, EP 1 070 703 and EP 597 107 and the contents of these patent applications are incorporated herein by reference.

Particular classes of IBAT inhibitors suitable for use in the present invention are benzothiepines, and the compounds described in the claims, particularly claim 1, of WO 00/01687, WO 96/08484 and WO 97/33882 are incorporated herein by reference. Other suitable classes of IBAT inhibitors are the 1,2-benzothiazepines, 1,4-benzothiazepines and 1,5-benzothiazepines. A further suitable class of IBAT inhibitors is the 1,2,5-benzothiadiazepines.

One particular suitable compound possessing IBAT inhibitory activity is (3*R*,5*R*)-3-butyl-3-ethyl-1,1-dioxido-5-phenyl-2,3,4,5-tetrahydro-1,4-benzothiazepin-8-yl β-D-glucopyranosiduronic acid (EP 864 582). Other suitable IBAT inhibitors include one of:
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(carboxymethyl) carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(carboxymethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-1'-phenyl-1'-[*N'*-(2-sulphoethyl)carbamoyl]methyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-sulphoethyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;
1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(5-carboxypentyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-carboxyethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(2-sulphoethyl)carbamoyl]-2-fluorobenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{(R)-1-[*N''*-(R)-(2-hydroxy-1-carboxyethyl)carbamoyl]-2-hydroxyethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-(carboxymethyl)carbamoyl] benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-(*N*-{α-[*N'*-((ethoxy)(methyl)phosphoryl-methyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3-butyl-3-ethyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(hydroxy)(methyl)phosphoryl]ethyl}carbamoyl)benzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N'*-(2-methylthio-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(methyl)(ethyl) phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-{*N*-[(R)-α-(*N'*-{2-[(methyl)(hydroxy) phosphoryl]ethyl}carbamoyl)-4-hydroxybenzyl]carbamoylmethoxy}-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[(R)-*N'*-(2-methylsulphinyl-1-carboxyethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methoxy-8-[*N*-{(R)-α-[*N'*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy]-2,3,4,5-tetrahydro-1,5-benzothiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthio-ethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxybutyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl) carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-(R)-hydroxypropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-sulphoethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxyethyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((R)-1-carboxy-2-methylthioethyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-{(S)-1-[*N*-((S)-2-hydroxy-1-carboxyethyl)carbamoyl]propyl}carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxy-2-methylpropyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-((S)-1-carboxypropyl) carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-[*N*-((R/S)-α-{*N*-[1-(R)-2-(S)-1-hydroxy-1-(3,4-dihydroxyphenyl)prop-2-yl]carbamoyl} -4-hydroxybenzyl)carbamoylmethoxy]-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]-4-hydroxybenzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine; and

1,1-Dioxo-3,3-dibutyl-5-phenyl-7-methylthio-8-(*N*-{(R)-α-[*N*-(2-(S)-3-(R)-4-(R)-5-(R)-2,3,4,5,6-pentahydroxyhexyl)carbamoyl]benzyl}carbamoylmethoxy)-2,3,4,5-tetrahydro-1,2,5-benzothiadiazepine;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of the compound of the present invention optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of one or more of the following agents selected from:

a CETP (cholesteryl ester transfer protein) inhibitor, for example those referenced and described in WO 00/38725 page 7 line 22 - page 10, line 17 which are incorporated herein by reference;

a cholesterol absorption antagonist for example azetidinones such as SCH 58235 and those described in US 5,767,115 which are incorporated herein by reference;

a MTP (microsomal transfer protein) inhibitor for example those described in Science, 282, 751-54, 1998 which are incorporated herein by reference;

a nicotinic acid derivative, including slow release and combination products, for example, nicotinic acid (niacin), acipimox and niceritrol;

a phytosterol compound for example stanols;

probucol;

an omega-3 fatty acid for example Omacor™;

an anti-obesity compound for example orlistat (EP 129,748) and sibutramine (GB 2,184,122 and US 4,929,629);

an antihypertensive compound for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an andrenergic blocker, an alpha andrenergic blocker, a beta andrenergic blocker for example metoprolol, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 blocker, a saluretic, a diuretic or a vasodilator;

a CB1 antagonist or inverse agonist for example as described in WO01/70700 and EP 65635 ;

aspirin;

a Melanin concentrating hormone (MCH) antagonist;

a PDK inhibitor; or

modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;

or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man, in need of such therapeutic treatment.

Particular ACE inhibitors or pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof, including active metabolites, which can be used in combination with the compound of the invention include but are not limited to, the following

compounds: alacepril, alatriopril, altiopril calcium, ancovenin, benazepril, benazepril hydrochloride, benazeprilat, benzoylcaptopril, captopril, captopril-cysteine, captopril-glutathione, ceranapril, ceranopril, ceronapril, cilazapril, cilazaprilat, delapril, delapril-diacid, enalapril, enalaprilat, enapril, epicaptopril, foroxymithine, fosfenopril, fosenopril, fosenopril sodium, fosinopril, fosinopril sodium, fosinoprilat, fosinoprilic acid, glycopril, hemorphin-4, idrapril, imidapril, indolapril, indolaprilat, libenzapril, lisinopril, lyciumin A, lyciumin B, mixanpril, moexipril, moexiprilat, moveltipril, muracein A, muracein B, muracein C, pentopril, perindopril, perindoprilat, pivalopril, pivopril, quinapril, quinapril hydrochloride, quinaprilat, ramipril, ramiprilat, spirapril, spirapril hydrochloride, spiraprilat, spiropril, spiropril hydrochloride, temocapril, temocapril hydrochloride, teprotide, trandolapril, trandolaprilat, utibapril, zabicipril, zabiciprilat, zofenopril and zofenoprilat. Preferred ACE inhibitors for use in the present invention are ramipril, ramiprilat, lisinopril, enalapril and enalaprilat. More preferred ACE inhibitors for uses in the present invention are ramipril and ramiprilat.

Preferred angiotensin II antagonists, pharmaceutically acceptable salts, solvates, solvate of such salts or a prodrugs thereof for use in combination with a compound of the invention include, but are not limited to, compounds: candesartan, candesartan cilexetil, losartan, valsartan, irbesartan, tasosartan, telmisartan and eprosartan. Particularly preferred angiotensin II antagonists or pharmaceutically acceptable derivatives thereof for use in the present invention are candesartan and candesartan cilexetil.

Therefore in an additional feature of the invention, there is provided a method for for the treatment of type 2 diabetes and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of the compound of the present invention in simultaneous, sequential or separate administration with an effective amount of one the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of the

compound of the present invention in simultaneous, sequential or separate administration with an effective amount of one the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises the compound of the present invention and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising the compound of the present invention and one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:
a) the compound of the present invention in a first unit dosage form;
b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:
a) the compound of the present invention together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
b) one of the other compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of the compound of the present invention of the present invention and one of the other compounds described in

this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the the treatment of metabolic syndrome or type 2 diabetes and its associated complications in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of the compound of the present invention and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of the compound of the present invention optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man, in need of such therapeutic treatment.

For the avoidance of doubt, "treatment" includes the therapeutic treatment, as well as the prophylaxis, of a condition.

The invention is illustrated, but in no way limited, by the following examples.

Examples

General Procedures

X-ray powder diffraction analysis (XRPD) was performed on samples prepared according to standard methods, for example those described in Giacovazzo, C. et al (1995),

Fundamentals of Crystallography, Oxford University Press; Jenkins, R. and Snyder, R. L. (1996), Introduction to X-Ray Powder Diffractometry, John Wiley & Sons, New York; Bunn, C. W. (1948), Chemical Crystallography, Clarendon Press, London; or Klug, H. P. & Alexander, L. E. (1974), X-ray Diffraction Procedures, John Wiley and Sons, New York. X-ray analyses were performed using a Siemens D5000 diffractometer and/or a Philips X'Pert MPD.

XRPD distance values may vary in the range ±2 on the last given decimal place.

Example 1

Preparation of 2-methylpropan-2-aminium (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate form III

The Form III of the salt of *Tert*-butylamine and (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate acid was crystallized from isopropyl acetate at 45°C.

To a solution of (*2S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid in isopropyl acetate (9.5 ml, 2g of acid), was added more isopropyl acetate (40 ml), followed by addition of *tert*-butylamine (0.93 ml), and water (0.24 ml). The solution was stirred at 45°C for 20 hrs, then the product (1.71 g) was filtered off, washed with isopropyl acetate (2X8 ml), and dried at ambient temperature. The product was confirmed with XRPD and DSC.

Example 2

Preparation of 2-methylpropan-2-aminium (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate form III

The Form III of the salt of *Tert*-butylamine and (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate acid was crystallized from isopropyl acetate and isooctane at 35°C.

To a solution of (2*S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (1.72 g) in isopropyl acetate (26 ml), *tert*-butylamine (0.4 ml) was added, followed by addition of some seeds (3.86 mg) and isooctane (26 ml). Then the solution was stirred at 35°C for at least 16 hrs, followed by a cooling down to 20°C in 2 hrs. The product (1.68 g) was filtered off and washed with isopropyl acetate/isooctane mixture (26 ml) and was dried in room temperature. The product was confirmed with NMR and XRPD.

Example 3

Preparation of 2-methylpropan-2-aminium (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate form III

The Form III of the salt of *Tert*-butylamine and (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate acid was crystallized from MiBK and isooctane at 55°C.

To a solution of (2*S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (2 g) in MIBK (30 ml), *tert*-butylamine (0.46 ml) was added at 55°C, followed by addition of isooctane (15 ml). Then some seeds (13.3 mg) and one more portion of isooctane (30 ml) was added. Then a cooling profile was started, from 55-30°C in 5 hrs, followed by ageing at 30°C for at least 13 hrs. The product (1.56 g) was filtered off and washed with MiBK/isooctane mixture (8 ml) and dried in vacuum/40°C. The product was confirmed with XRPD.

Example 4

Preparation of 2-methylpropan-2-aminium (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate form III

The Form III of the salt of *tert*-butylamine and (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate acid was recrystallized from isopropyl acetate and isooctane at 72°C.

The salt (3 g) was dissolved in isopropyl acetate (39 ml) at 72°C, followed by filtration, washing the filter with isopropyl acetate (6 ml) and addition of isooctane (45 ml). Then a cooling profile was started, from 72-20°C in 5 hrs. The product (2.07 g) was filtered off and washed with isopropyl acetate/isooctane mixture (12 ml) and dried in vacuum/40°C. The product was confirmed with XRPD.

Example 5

Preparation of 2-methylpropan-2-aminium (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate form III

The Form III of the salt of *Tert*-butylamine and (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate acid was crystallized from isopropyl acetate and isooctane at 72°C.

To a solution of (*2S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (2.97 g) in isopropyl acetate (11 ml), more isopropyl acetate (29 ml) was added. Then *tert*-butylamine (1mol/l, 6.55 ml) was added at 40°C, followed by addition of a portion of seeds (142.8 mg), which all dissolved, followed by addition of isooctane (30 ml) and then heating to 72°C, whereafter a cooling profile is started: 72-30°C/4 hrs, ageing at 30°C for 13 hrs. At 64°C one more portion of seed (60

mg) was added and the precipitation starts. The product (2.77 g) was filtered off and washed with isopropyl acetate (22 ml) and dried in vacuum/25°C. The product was confirmed with XRPD and NMR.

Example 6

Preparation of 2-methylpropan-2-aminium (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate Form II

The Form II of the salt of Tert-butylamine and (2S)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate acid was crystallized from isopropyl acetate at -10°C.

To a solution of (*2S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (1.75g) in isopropyl acetate (8 ml), *tert*-butylamine (1.2 mole equivalents, 0.2 mol/l) was added at -10°C. Then addition of some seed, (1.0 w/w%) of Form I, was done. Then the solution was stirred at-10°C for at least 19 hrs. The product (1.05 g) was filtered off and washed with isopropyl acetate (14 ml) and was dried in vacuum/40°C for about 20 hrs. The product (Form II) was confirmed with XRPD.

Example 7

Reference Example Form I prepared according to prior art (WO 2004/110984 A1, Ex. 6)***tert*-butylamine salt of (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid, now referred to as "Form I".**

(*2S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid (0,49 g) and *tert*-butylamine (0,077 g) were mixed in acetone(8 ml/g), followed by addition of isooctane (8 ml/g) and stirred at room temperature. The product (0.36 g) was filtered off

and washed with isooctane (4 ml/g) and was dried in room temperature. The product was confirmed with NMR and XRPD.

^{1}H-NMR (400 MHz, $CDCl_3$):
7.3-7.0 (7H, m), 6.7 (1H, d), 6.6 (1H, d), 4.6 (1H, s), 4.3 (1H, s), 3.7 (1H, m), 3.6 (1H, m), 3.5 (2H, m), 3.3 (1H, t), 3.1 (2H, m), 2.9 (1H, m), 2.7 (3H, m), 1.5 (2H, br m), 1.3 (9H, br s), 1.2 (6H, br s), 1.0 (3H, t), 0.8 (3H, m)

Example 8

Preparation of 2-methylpropan-2-aminium (2*S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate Form II

The Form II of the salt of Tert-butylamine and (2S)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoate acid was crystallized from isopropyl acetate and isooctane at ambient temperature.

To a solution of (*2S*)-2-Ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid in isopropyl acetate (120 ml), was added *tert*-butylamine (1.86 ml) at ambient temperature. Then isooctane (60 ml) was added, followed by seeding with Form I (85 mg) and one more portion of isooctane (60 ml). The slurry was stirred at ambient temperature for at least 23 hrs. The product (4.46 g) was filtered off and washed with isopropyl acetate/isooctane 1/1 (24 ml), and was dried in vacuum/40°C for about 21 hrs. The product (Form II) was confirmed with XRPD.

CLAIMS

1. Form III of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid, characterized in providing an X-ray powder diffraction pattern exhibiting peaks at substantially the following d-values: 4.77, 5.6, 6.0, 8.2 and 19.0 Å.

2. Form III of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid, characterized in providing an X-ray powder diffraction pattern exhibiting peaks at substantially the following d-values: 3.81, 4.48, 4.57, 4.77, 5.3, 5.4, 5.6, 5.7, 6.0, 8.2, 11.6 and 19.0 Å.

3. Form III of the tert-butylamine salt of (2S)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid, characterized in providing an X-ray powder diffraction pattern exhibiting peaks at substantially the following d-values: 3.05, 3.30, 3.75, 3.81, 4.08, 4.26, 4.34, 4.44, 4.48, 4.57, 4.77, 5.00, 5.3, 5.4, 5.6, 5.7, 6.0, 8.2, 11.6 and 19.0 Å.

4. A process for the preparation of the tert-butylamine salt of (2S)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid form III as defined in any of claims 1-3, comprising the steps of:

I) having the (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid dissolved in a suitable solvent or solvent mixture and adding tert-butylamine

II) optionallly adding an anti-solvent or anti-solvent mixture

III) adjusting the temperature to a temperature at or above 35°C

IV) stirring for at least 15-25 hours or more

V) separating off the product

VI) optionally washing with a suitable solvent

VII) drying the product.

5. A process for the preparation of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid form III as defined in any of claims 1-3, comprising the steps of:

I) having the (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid dissolved in a suitable solvent or solvent mixture and adding tert-butylamine

II) optionallly adding an anti-solvent or anti-solvent mixture

III) adjusting the temperature to a temperature at or above 35°C

IV) seeding with Form III at any stage after step I)

V) cooling the mixture slowly at a temperature decreasing rate not higher than 15°C/hour

VI) separating off the product

VII) optionally washing with a suitable solvent

VIII) drying the product

6. A process for the preparation of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid form III as defined in any of claims 1-3, comprising the steps of:

I) having the (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid dissolved in a suitable solvent or solvent mixture and adding tert-butylamine

II) optionallly adding an anti-solvent or anti-solvent mixture

III) adjusting the temperature to a temperature at or above 35°C

IV) cooling the mixture slowly at a temperature decreasing rate not higher than 15°C/hour

V) separating off the product

VI) optionally washing with a suitable solvent

VII) drying the product

7. A process for the preparation of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid form III as defined in any of claims 1-3, comprising the steps of:

I) having the (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid dissolved in a suitable solvent or solvent mixture and adding tert-butylamine

II) optionallly adding an anti-solvent or anti-solvent mixture

III) adjusting the temperature to a temperature at or above 35°C

IV) stirring for at least 15-25 hours or more

V) cooling the mixture slowly at a temperature decreasing rate not higher than 15°C/hour

VI) separating off the product

VII) optionally washing with a suitable solvent

VIII) drying the product

8. A process for the preparation of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid form III as defined in any of claims 1-3, comprising the steps of:

I) having the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid or any polymorpic form thereof dissolved in a suitable solvent or solvent mixture

II) adjusting the temperature to a temperature at or above 35°C

III) optionallly adding an anti-solvent or anti-solvent mixture

IV) cooling the mixture slowly at a temperature decreasing rate not higher than 15°C/hour

V) optionally washing with a suitable solvent

VI) drying the product

9. A process for the preparation of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid form III as defined in any of claims 4-8, wherein the ratio of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid to tert-butylamine is from 0.8:1 to 1.2:1 on equivalents basis.

10. A process for the preparation of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid form III as defined in

any of claims 4-8, wherein the ratio of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid to tert-butylamine is from 0.9:1 to 1.1:1 on equivalents basis.

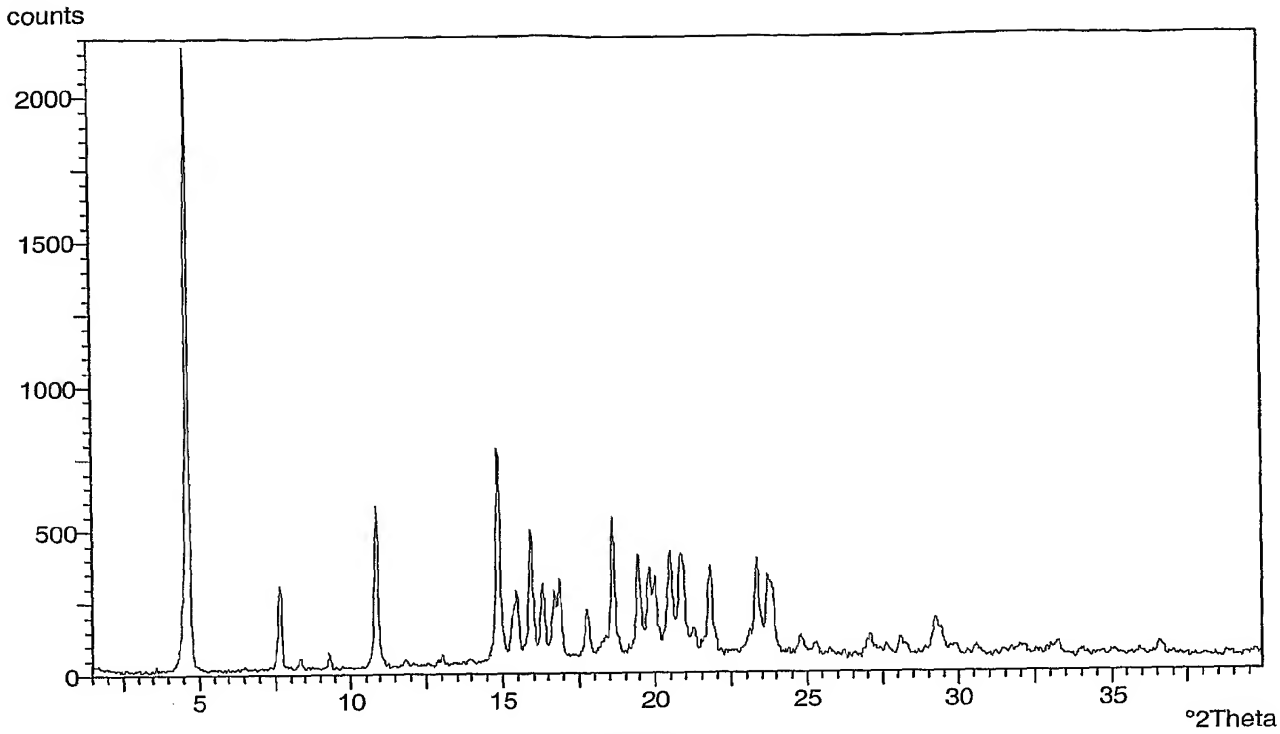
11. A process for the preparation of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid form III as defined in any of claims 4-8, wherein the ratio of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino]-2-oxoethoxy}phenyl)propanoic acid to tert-butylamine is from 0.95:1 to 1.05:1 on equivalents basis.

12. A pharmaceutical formulation comprising Form III of the tert-butylamine salt of (2S)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid, as defined in any of claims 1-3, in admixture with at least one pharmaceutically acceptable excipient.

13. The use of the Form III of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid as defined in any of claims 1-3, in therapy.

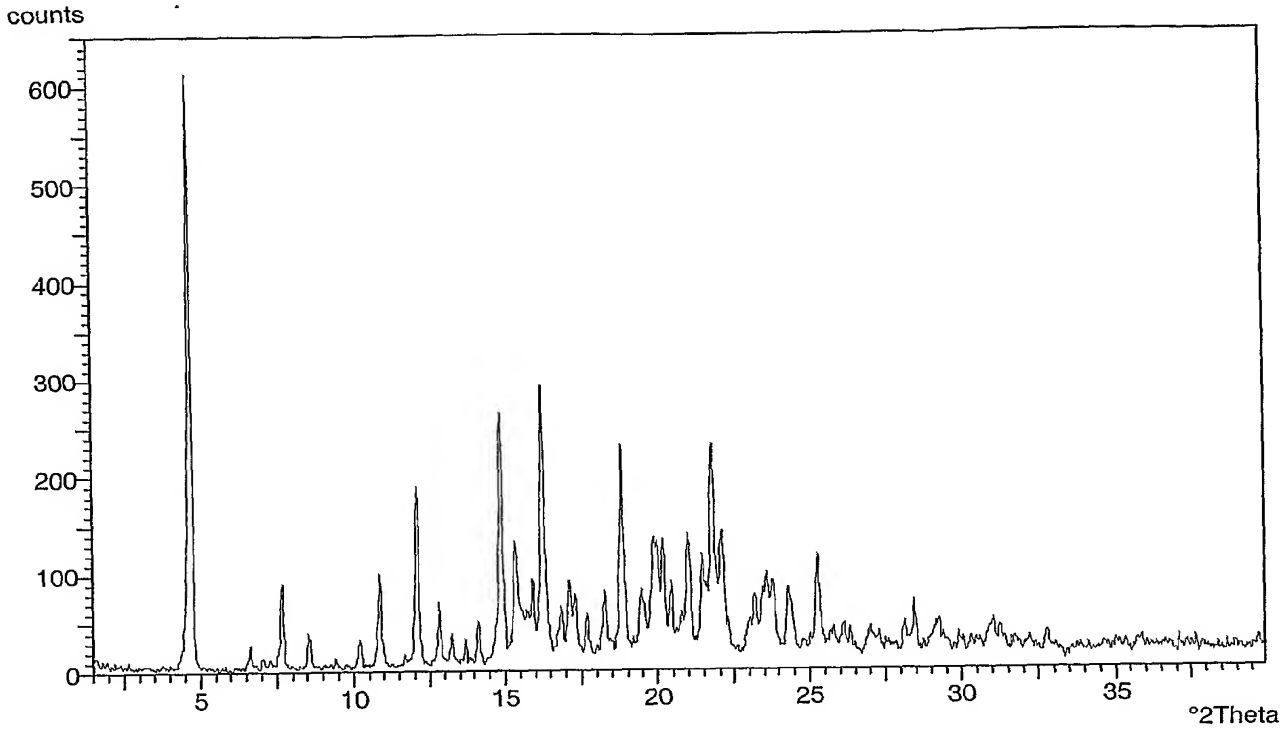
14. The use of the Form III of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid as defined in any of claims 1-3, as active ingredient in the manufacture of a medicament for use in treatment of lipid disorders (dyslipidemias) whether or not associated with insulin resistance or with other manifestations of the metabolic syndrome.

15. A method of treatment of lipid disorders (dyslipidemias) whether or not associated with insulin resistance or with other manifestations of the metabolic syndrome, which comprises administration of a therapeutically effective amount of Form III of the *tert*-butylamine salt of (*2S*)-2-ethoxy-3-(4-{2-[hexyl(2-phenylethyl)amino-2-oxoethoxyphenyl)propanoic acid as defined in any of claims 1-3, to a patient suffering therefrom.



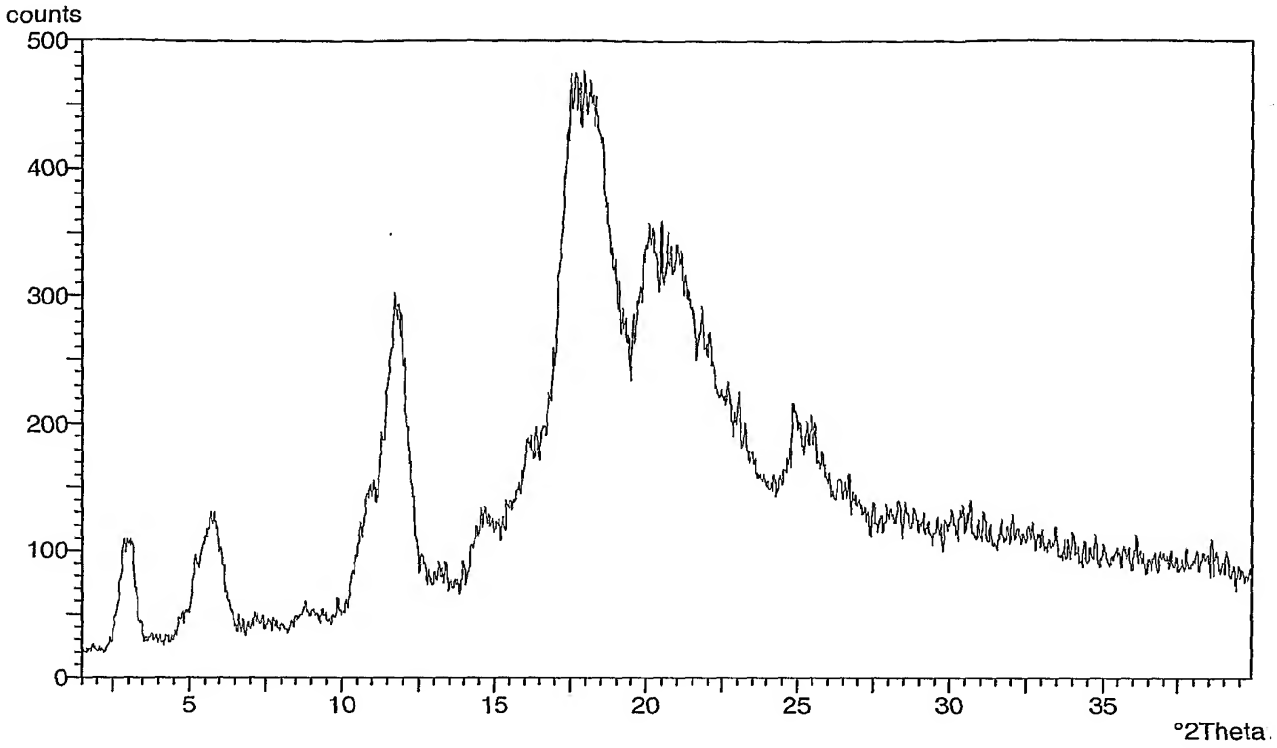
Form III.

Figure 1/3.



Form I.

Figure 2/3.



Form II.

Figure 3/3.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000825

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07C, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CA, BIOSIS, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03051821 A1 (ASTRAZENECA AB), 26 June 2003 (26.06.2003), claim 2 --	1-15
A	WO 2004056748 A1 (ASTRAZENECA AB), 8 July 2004 (08.07.2004), claim 1 --	1-15
A	WO 2004110982 A1 (ASTRAZENECA AB), 23 December 2004 (23.12.2004), claim 7 --	1-15
A	WO 2004110984 A1 (ASTRAZENECA AB), 23 December 2004 (23.12.2004), claim 6 --	1-15

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 August 2006	05 -10- 2006
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Fernando Farieta/Eö Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/000825

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004110985 A1 (ASTRAZENECA AB), 23 December 2004 (23.12.2004), claim 1 ---	1-15
A	WO 2004113270 A2 (ASTRAZENECA AB), 29 December 2004 (29.12.2004), claim 1 --- --------	1-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE06/000825

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 15
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 15 relates to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods /Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compound.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

International patent classification (IPC)

C07C 235/20 (2006.01)
A61K 31/16 (2006.01)
A61P 3/00 (2006.01)

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Use the application number as username.
The password is **CFLDPUTTFA**.

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

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				MX	PA05006812	A	08/09/2005
				NO	20052914	A	19/07/2005
				RU	2005117792	A	27/01/2006
				US	20050131068	A	16/06/2005
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				CA	2528933	A	23/12/2004
				EP	1638920	A	29/03/2006
				GB	0314134	D	00/00/0000
				MX	PA05013715	A	08/03/2006
				NO	20055924	A	05/01/2006
				US	20060142392	A	29/06/2006
WO	2004110984	A1	23/12/2004	AU	2004247610	A	23/12/2004
				CA	2528932	A	23/12/2004
				EP	1638922	A	29/03/2006
				GB	0314129	D	00/00/0000
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				US	20060142389	A	29/06/2006
WO	2004110985	A1	23/12/2004	AU	2004247611	A	23/12/2004
				BR	PI0411455	A	18/07/2006
				CA	2527608	A	23/12/2004
				EP	1638921	A	29/03/2006
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